Evaluation of Outer Retinal Microstructure in Eyes with Epiretinal Membrane and Macular Hole

Maküla Deliği ve Epiretinal Mebranlı Gözlerde Dış Retinal Mikroyapının Değerlendirilmesi

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ABSTRACT

Purpose: To evaluate the outer retinal microstructure via spectral-domain optical coherence tomography (SD-OCT) in patients with vitreoretinal interface abnormalities.

Materials and Methods: Twenty-three patients with unilateral epiretinal membrane (ERM) and 17 patients with unilateral macular hole (MH) were included to the study. Outer retinal microstructure was evaluated with SD-OCT, and integrity of external limiting membrane, ellipsoid zone, and the interdigitation zone as well as retinal thickness scores were noted for each study eye.

Results: Mean age and gender were not different between patients with ERM and MH. Higher retinal thickness was found in eyes with ERM at 500 µm and 1000 µm distances to the fovea in both nasal and temporal quadrants. The integrity of interdigitation zone was significantly more frequent in eyes with ERM when compared to eyes with MH, and the difference was clearer in nasal quadrant compared with temporal quadrant of the fovea. Both ellipsoid zone and external limiting membrane integrity were not statistically different between eyes with ERM and MH.

Conclusion: Outer retinal microstructures between eyes with ERM and MH have some differences; better knowledge of these changes might have importance on the surgical plans of such diseases.

Key Words: Interdigitation zone, epiretinal membrane, external limiting membrane, ellipsoid zone, macular hole.

ÖZ

Amaç: Vitreoretinal ara yüzey anormallikleri olan hastalarda spektral-domain optik koherens tomografi (SD-OKT) ile dış retinal mikroyapıyı değerlendirmek.

Gereç ve Yöntem: Tek taraflı epiretinal membranlı (ERM) 23 hasta ve tek taraflı maküler delikli (MD) 17 hasta çalışmaya dahil edildi. Dış retina mikroyapısı SD-OKT ile değerlendirildi ve her çalışma gözü için retinal kalınlık skorları yanısıra dış sınırlayıcı membran, elipsoid zon ve interdijitasyon zonu bütünlüğü kaydedildi.

Bulgular: Ortalama yaş ve cinsiyet, ERM ve MD'li hastalar arasında farklı değildi. Hem nazal hem de temporal kadranlarda foveaya 500 µm ve 1000 µm'lik mesafelerde ERM'li gözlerde daha yüksek retinal kalınlık bulundu. İnterdijitasyon zonu bütünlüğü, MD'li gözlerle karşılaştırıldığında, ERM'li gözlerde anlamlı derecede daha sıktı ve foveanın temporal kadranı ile karşılaştırıldığında nazal kadranda fark daha belirgindi. Hem elipsoid zon hem de dış sınırlayıcı membran bütünlüğü, ERM ve MD'li gözler arasında istatistiksel olarak farklı değildi.

Sonuç: ERM ve MD'li gözler arasında dış retinal mikroyapılar bazı farklılıklara sahiptir; Bu değişikliklerin daha iyi anlaşılması, bu tür hastalıkların cerrahi planlarında önemli olabilir.

Anahtar Kelimeler: İnterdijitasyon zonu, epiretinal membran, dış sınırlayıcı membran, elipsoid zon, maküla deliği.

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Geliş Tarihi - Received: 21.11.2017
Kabul Tarihi - Accepted: 02.01.2018
Ret-Vit 2018; 27: 259-264

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INTRODUCTION

Epiretinal membrane (ERM) and macular hole (MH) are common vitreoretinal interface diseases that may be caused by anomalous posterior vitreous detachment (PVD) and vitreoschisis.[1-6] However, cell component and structure of the remained vitreous which is attached to the internal limiting membrane (ILM) are different between ERM and MH. Moreover, remained vitreopapillary adhesions cause a very important difference in the vectorial force of MH and ERM.[7] Since the changes in vitreoretinal interface and vitreoretinal adhesions are different in ERM and MH, there may be some differences between ERM and MH in regard to outer retinal microstructures hence there is a very little information about the condition of outer retinal structures in such diseases.

Although conventional time-domain optic coherence tomography (OCT) remains limited data on delineating subtle pathologic changes, spectral domain OCT (SD-OCT), with its high resolution of up to 5 μm and high scanning speed, has allowed layer-by-layer evaluation of the retina. The images of the SD-OCT clearly show three highly reflective layers in the outer retina; which are the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ).[8,9] The aim of this study was to evaluate the changes in ELM, EZ and IZ of the eyes with ERM and MH.

MATERIAL AND METHODS

This retrospective, comparative study was designed to include a total of 23 patients with unilateral ERM (57.5%) and 17 patients with unilateral MH (42.5%). Patients were recruited from the records of the Vitreoretinal Department of the Dokuz Eylul University Hospital, Izmir, Turkey between January 2014 and May 2015. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and all of the patients consented to our review of their medical records.

This study included patients with idiopathic ERM and MH with symptomatic visual impairment, metamorphopsia, and decreased visual acuity. All MHs were diagnosed with a stage 2, 3, or 4 idiopathic macular hole according to the Gass classification. Seven eyes had stage 2, 6 eyes had stage 3 and 4 eyes had stage 4 macular hole. Eyes with secondary ERM and MH resulting from diabetic retinopathy, retinal detachment surgery, trauma, retinal vein occlusion, uveitis, and those with eccentric type of disease were excluded from the study. The patients underwent comprehensive ophthalmologic examinations including best-corrected visual acuity (BCVA) assessments, slit-lamp biomicroscopy, dilated fundoscopy, fundus color photography, and SD-OCT scans (Spectralis II, OCT+HRA; Heidelberg Engineering, Heidelberg, Germany). The images were generated using the horizontal SD-OCT cross-section (14 lines spaced 250 μm apart). In order to get the maximum quality, 25–30 frames were averaged for each B-scan. Best corrected visual acuity was measured with Snellen acuity chart. We used the segmentation software which was detected the ELM, EZ, the IZ. Scans were obtained by an experienced OCT examiner at least two times to obtain images with a signal intensity of seven or more. The assessment of the outer layer abnormality of the fovea was made by two observers who were masked to any clinical information (EK and MK). We controlled a possible bias in OCT scans, using the manufacturer's proprietary software. Each observer was masked to the other observer's readings. The measurements were performed in a random order and masked fashion. The intraobserver and interobserver reproducibility of the RT measurements was assessed by measuring the intraclass correlation coefficient (ICC). To assess intraobserver reproducibility, one observer remeasured RT using the first OCT session for a random sample of 20 eyes approximately 1 month after all sets of measurements were completed, while remaining masked to the original measurements. The signals from the photoreceptor layer including the ELM line, EZ, and IZ were graded as intact or absent at 500 μm, 1000 μm, and 2000 μm distances to the foveal center in nasal and temporal quadrants as described in detail elsewhere.[10-12] In brief, the photoreceptor layer of the SD-OCT images was classified as having an intact line when a continuous or disrupted reflective line was observed. When the signal was not observed, it was categorized as absent. The retinal thickness (RT) was defined as the distance between inner retinal surface and inner border of retinal pigment epithelium at fovea.

The statistical analysis was performed with SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois, USA). Eyes with ERM and MH were compared regarding the presence of ELM, EZ and IZ with chi-square test and with independent t-test regarding BCVA and RT. A p value of below 0.05 was considered as significant.

RESULTS

Mean age was 64.4 ± 7.8 years (range, 44 to 78 years) in the group of ERM, and 68.2 ± 6.4 years (range, 54 to 79 years) in the group of MH (p=0.107). Ten of the 23 patients (43.5%) were male in ERM group, whereas 3 of the 17 patients (17.6%) were male in the MH group (p=0.085). Duration of the symptoms was 2.6 ± 0.5 months (range, 1 to 11 months) and 2.4 ± 0.6 months (range, 1 to 12 months) in ERM and MH groups, respectively (p=0.309). Mean BCVA was 0.38 ± 0.10 in ERM group and 0.36 ± 0.24 in MH group (p=0.377). Retinal thickness was higher in ERM group at 500 and 1000 μm distances to the fovea in both nasal and temporal quadrants that were shown in Table 1.

Frequency of IZ integrity was significantly higher in eyes with ERM when compared to eyes with MH. Figure 1 demonstrates intact IZ in eye with ERM and figure 2 demonstrates an eye with grade 2 macular hole in which IZ was not

Table 1. *Retinal thicknesses at all quadrants*

	Group	Mean	Std. Deviation	P value
Nasal 500µm	**ERM**	480.26	108.97	0.406
	MH	455.88	56.74	
Nasal 1000µm	**ERM**	449.17	96.94	0.004*
	MH	372.64	40.018	
Nasal 1500µm	**ERM**	371.95	67.39	0.001*
	MH	310.64	34.68	
Temporal 500µm	**ERM**	479.95	134.66	0.150
	MH	429.29	52.14	
Temporal 1000µm	**ERM**	432.34	104.61	0.003*
	MH	347.64	45.66	
Temporal 1500µm	**ERM**	347.95	76.89	0.008*
	MH	292.11	35.49	

*Statistically significant, **ERM:** Epiretinal membrane, **MH:** Macular hole

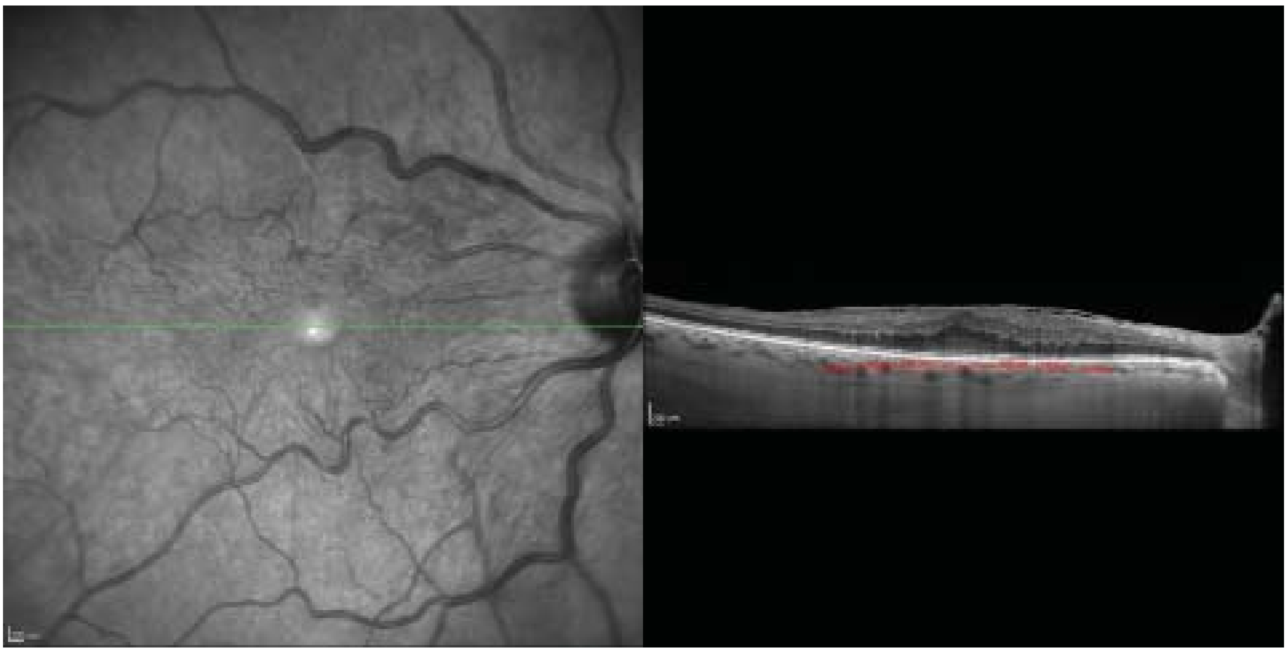

Figure 1. *Intact interdigitation zone at all quadrants in an eye with epiretinal membrane.*

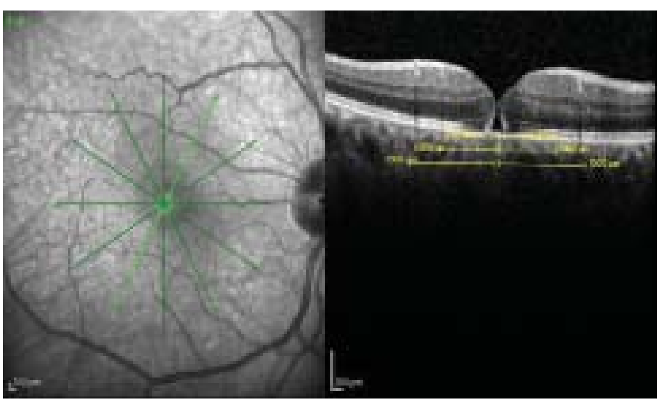

Figure 2. *Absent interdigitation zone at 500 µm distance to the foveal center at nasal and temporal quadrants.*

observed in 500 µm distance to the foveal center at nasal and temporal quadrant. This difference was clearer in nasal quadrant compared with temporal quadrant. Both the ELM and EZ integrity rates were not statistically different in eyes with ERM and MH. Integrity rates of ELM, EZ and IZ at various quadrants of the fovea in our study eyes were summarized in Table 2.

DISCUSSION

The importance of PVD and vitreoretinal interface is established for the development of ERM and MH. If the posterior vitreous cortex splits (vitreoschisis) during PVD process, there can be differences upon the level of such split. Vitre-

Table 2. *Integrity rates of external limiting membrane, ellipsoid zone and interdigitation zone*

	ERM(n=23)	MH (n=17)	p value
IZ (%)			
Nasal 500 µm	73.9	5.9	<0.001*
Nasal 1000 µm	73.9	23.5	0.002*
Nasal 1500 µm	73.9	29.4	0.005*
Temporal 500 µm	60.9	5.9	<0.001*
Temporal 1000 µm	60.9	29.4	0.049*
Temporal 2000 µm	69.6	35.3	0.031*
EZ (%)			
Nasal 500 µm	87.0	82.4	0.687
Nasal 1000 µm	95.7	88.2	0.379
Nasal 1500 µm	100	94.1	0.239
Temporal 500 µm	87.0	76.5	0.388
Temporal 1000 µm	95.7	82.4	0.166
Temporal 2000 µm	100	94.1	0.239
ELM (%)			
Nasal 500 µm	87.0	88.2	0.904
Nasal 1000 µm	87.0	88.2	0.622
Nasal 1500 µm	87.0	100	0.122
Temporal 500 µm	87.0	88.2	0.904
Temporal 1000 µm	87.0	94.1	0.455
Temporal 2000 µm	87.0	94.1	0.455

*Statistically significant, **ERM:** Epiretinal membrane, **MH:** Macular hole, **IZ:**Interdigitation zone, **EZ:** Ellipsoid zone, **ELM:**External limiting membrane.

oschisis anterior to the level of the hyalocytes leaves a relatively thick cellular membrane attached to the macula. If there is also separation from the optic disc (present in 82% of the cases), inward (centripetal) contraction of this membrane may induce macular pucker. If the split occurs at a level posterior to the hyalocytes, the remaining premacular membrane is relatively thin and hypocellular. Persistent vitreopapillary adhesions (VPA) that present in 87.5% of cases, influences the vector of in the tangential plane, resulting in outward (centrifugal) tangential traction (especially nasal), inducing a macular hole.[7]

Although, the vitreoretinal surface and VPA are well studied in the pathogenesis of ERM and MH, there are only few studies about the condition of outer retinal structures. The recovery of these structures in the OCT images after surgery for an ERM[8], MH[13-16], diabetic macular edema[17,18] and rhegmatogenous retinal detachment[19] was significantly correlated with BCVA.

Shimozono et al.[20] studied 50 eyes of 49 patients who underwent vitrectomy for idiopathic ERM. Authors categorized the eyes into 3 groups: Group A, with a continuous EZ and IZ; Group B, with a continuous EZ but disrupted IZ; and Group C, with a disrupted EZ and IZ. At 6 months, Group A showed a significantly better BCVA than Group B, and poorer BCVA was noted in Group C. Defect diameters of EZ and IZ were also significantly correlated with BCVA postoperatively. Itoh et al.[16]evaluated the presence and intactness of the IZ by SD-OCT and compared with the presence of the EZ and the ELM at 1,3, 6, 9, and 12 months after the MH surgery. They found that the BCVA was >20/25 at 12 months in 91% of the eyes with a distinct or irregular IZ but in only 44% of the eyes without a IZ. They concluded that the significant correlation between the BCVA and a distinct or irregular IZ after successful MH surgery indicates that the recovery of foveal cone microstructure is associated with good postoperative BCVA. In another study, Itoh et al.[15] investigated whether the postoperative length of the IZ defect is significantly correlated with BCVA after MH closure. The recovery of the foveal IZ defect was related to visual recovery after MH closure and they postulated that the length of the preoperative IZ defect may predict the BCVA after macular hole surgery. Itoh et al.[21] reported that the recovery of the foveal IZ defect was correlated with the BCVA also after ERM surgery. In the present study, we found that the IZ was significantly more disrupted in eyes with MH when compared with eyes with ERM. These findings are consistent with the previous findings about the vectorial forces of such diseases (centripetal in ERM, and centrifugal in MH). According to the persistent VPA that was present in 87.5% of eyes with MH, theoretically the disruption of IZ might be higher in nasal quadrant than temporal quadrant. In the current study, the presence rate of IZ integrity was slightly higher in temporal quadrant when compared with nasal quadrant but this difference was not statistically significant. Houly et al.[22] investigated the correlation between the length of ELM, EZ and IZ defects and visual prognosis in patients undergoing macular hole (MH) surgery stated that the preoperative length of the ELM defect is the strongest predictor of visual acuity after MH surgery. Okamoto et al.[23] designed a study to examine any relationship between aniseikonia and the foveal microstructure and found that preoperative aniseikonia was associated with MH size and the defect length of ELM.

Whether peeling of ILM or not remains controversial. Some studies have suggested that removal of the ILM along with ERM produced better outcomes in visual acuity and less recurrence rates than ERM peeling alone.[24,25] However, others reported that eyes treated with ILM removal together with ERM removal had a less favorable visual outcome than eyes that had only ERM removal.[26-28]

In our study, we demonstrated that the photoreceptor integrity is highly protected in eyes with ERM and probably the ILM peeling causes an iatrogenic disruption in these eyes. As a result, we believe that a detailed evaluation of outer retinal structures in eyes with ERM is mandatory to determine the surgical intervention.

Although the small sample size is the main limitation of our study, findings of our study give important information about the outer retinal microstructure in patients with ERM and MH. Similar visual acuity scores might be resulted by small sample size of the study. Furthermore, as macular hole and ERM have different pathogenesis two articles investigate macular hole and ERM separately would be very useful to better understand the pathogenesis of these diseases. The authors of this study are aware that the findings of this study are compared to previous studies performing surgical therapy, although there is no surgical treatment performed in current study. Unfortunately, studies investigated the outer retinal structures in macular hole or ERM were concentrated to the effect of the preoperative and postoperative condition of outer retinal structures on postoperative and this was limitate us to compare our results with similarly designed previous studies. More studies with larger sample sizes will strengthen the value of our study.

Funding: No funding was received for this research.

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers'bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Contributors Conception and design: EK and OK; acquisition of data: EK; analysis and interpretation of data: EK, DD, TO, MK and NK; article drafting and revising: OK, EK; final approval: SK, NK and EK.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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